Thrombophilias: Maternal and Fetal Complications

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LEARNING OBJECTIVES

After this lecture, the practicing MFM specialist should:

1. Know the most common inherited thrombophilias.
2. Appreciate the role that family history plays in assessing maternal thrombotic risk.
3. Understand the role of ultrasound and fetal testing in this setting.

This speaker has no significant financial interests or other relationships with industry relative to the subject of this lecture.
Inherited Thrombophilias

• Hemostasis 101: clotting cascade and changes with pregnancy
• Genetics, Prevalence and Diagnosis of Thrombophilias
• Risk of Maternal Thrombosis
• Risk of Adverse Pregnancy Outcomes
Hemostatic and Fibrinolytic Pathways
Anticoagulant Pathway

- IX → IXa /platelets
- X → IXa
- TF/VII → TFPI
- Xa → VIIIa (APC/S)
- Xa → (-) PZ/ZPI
- IIa → Va
- Va → II (APC/S)
Anticoagulant Pathway

IX → IXa

TX / platelets

TF/II

XIa

VIIIa (APC/S)

Xa (-) PZ/ZPI & AT

Ta

Antithrombin
+- heparin

Fibrinogen

FXIII

PAI-1

TAFI

Antiplasmin

FDP

Fibrinogen

+ tPA

Plasmin

tPA
Tissue Factor Immunohistochemistry
<table>
<thead>
<tr>
<th>Pregnancy-Associated Changes in Hemostatic and Fibrinolytic Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase in Clotting Factors:</strong></td>
</tr>
<tr>
<td>20 to 1000% increase in levels of fibrinogen and factors II, VII, VIII, X and XII</td>
</tr>
<tr>
<td><strong>Decrease in Anticoagulant and Fibrinolytic Activity:</strong></td>
</tr>
<tr>
<td>Protein S levels (free and total) decrease by 40%</td>
</tr>
<tr>
<td>PAI-1 levels increase two to three-fold in pregnancy</td>
</tr>
</tbody>
</table>
Maternal Risks of VTE in Pregnancy

Pregnancy is associated with a 5 to 10-fold increased risk of venous thromboembolism (VTE)

Prevalence of VTE in pregnancy is about 1/1500

6-week Postpartum period associated with a 3-fold higher risk of VTE and 8-fold higher risk of APE with 80% of fatal PEs occurring after a C-section

Common Inherited Thrombophilias Caused by Discrete Mutations

- Factor $V^{\text{Leiden}}$ mutation
- Prothrombin$^{G20210A}$ mutation
- $\text{MTHFR}^{C677T \& A1298C}$ mutations causing hyperhomocysteinemia
Inherited Thrombophilias Caused by Multiple Mutations

- Antithrombin (AT) deficiency
- Protein C (PC) deficiency
- Protein S (PS) deficiency
Lesser Thrombogenic Thrombophilic Mutations

Protein Z and ZPI deficiency
4G/4G PAI-1 mutation
Factor V H1299R polymorphism
factor VII-121del/ins polymorphism
β-fibrinogen-455 G-A polymorphism
apolipoprotein B R3500Q and E2/E3/E4
factor XIII V34L
GPIIIa L33P
HFE C282Y

A) **Factor V$^{\text{Leiden}}$ mutation**

Caused by a G$\rightarrow$A mutation in nucleotide 1691 of the factor V gene, resulting glutamine $\rightarrow$ arginine switch at position 506 which impairs APC inactivation:

- prevalence 5%-10% of Europeans
- prevalence of 3% in African-Americans but rare in Asian and African populations

*Zotz et al., Best Pract Res Clin Haematol 2003;16:243-59*
B) Prothrombin$^{G20210A}$ mutation (PGM)

• Mutation in promoter region causes increased gene transcription 2 to 3-fold, increasing protein levels

• Prevalence 2-3% in European pop.

C) Hyperhomocysteinemia (HHC)

Inheritance:
- Heterozygosity for CBS (0.3-1.4% of European pop.)
- Homozygosity for MTHFR C677T & A1298C polymorphisms (prevalence 10-16% and 4-6%, respectively among Europeans)

Phenotype
- Since fortification of U.S. flour with folate, HHC is virtually never seen in general population.

D) Antithrombin deficiency

• > 260 mutations can result in decreased antigen +/or activity levels (Types I vs. II)

• Prevalence varies with activity cut off employed:
  < 80% = 2.6%
  < 60% = 0.02%

E) **Protein C Deficiency:**

- > 240 mutations result in decreased PC antigen +/- activity levels (Type I vs. II)

- Prevalence varies with functional assay activity cut off:
  - < 70% = 3.9% of population
  - < 50% = 0.3% of population

F) **Protein S Deficiency:**

Three phenotypes:

1) Decreased total and free Antigen (Ag) and activity (66%)

IIa) Normal Ag with decreased activity (rare)

IIb) Normal Ag decreased free PS and activity (33%)

F) **Protein S Deficiency:**

Screening associated with wide inter- & intra-assay variability (20-40%) due variations in factor VIII, free PS levels and C4b BP (latter increases with surgery, infections & pregnancy decreasing free PS levels)

Identifying low free protein S levels (< 55% in non-pregnant women; < 29% in 1st & 2nd tri, < 24% in 3rd tri) appears to best correlate with genetic deficiency

Beauchamp et al., Br J Haematol 2004;125:647-54;
Hermida et al., Thromb Haemost 1999; 82:1634–1638_
F) Protein S Deficiency

- Prevalence based on low free PS Antigen (Ag) levels = 0.2 to 0.5%
- Prevalence when detected by functional activity level < 55% = 4.8%

Beauchamp et al., Br J Haematol 2004; 125:647-54;
Goodwin et al., Arch Pathol Lab Med 2002; 126:1349-66.
## Risk of maternal VTE for a given thrombophilia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>VTE Risk No Hx</th>
<th>VTE Risk (+) Hx</th>
<th>% of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL (heteroz.)</td>
<td>0.2%</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>FVL (homoz.)</td>
<td>1.5%</td>
<td>17%</td>
<td>2.2%*</td>
</tr>
<tr>
<td>PGM (heteroz.)</td>
<td>0.5%</td>
<td>&gt;10%</td>
<td>17%</td>
</tr>
<tr>
<td>PGM (homoz.)</td>
<td>2.8%</td>
<td>&gt;17%</td>
<td>0.5%*</td>
</tr>
<tr>
<td>FVL/PGM</td>
<td>4.7%</td>
<td>&gt;20%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Disorder</td>
<td>VTE Risk No Hx</td>
<td>VTE Risk (+) Hx</td>
<td>% of VTE</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------</td>
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<td>----------</td>
</tr>
<tr>
<td>AT def activity &lt; 60%</td>
<td>7.2%</td>
<td>40%</td>
<td>1%</td>
</tr>
<tr>
<td>PC def activity &lt; 50%</td>
<td>0.8%</td>
<td>4-17%</td>
<td>14%</td>
</tr>
<tr>
<td>PS def free Ag &lt; 55%</td>
<td>0.1%</td>
<td>0-22%</td>
<td>3%</td>
</tr>
<tr>
<td>HHC &gt; 16uM No risk with just MTHFR mutation</td>
<td>0.2%*</td>
<td>NA</td>
<td>&lt; 5%*</td>
</tr>
</tbody>
</table>
**Maternal Risks of Thrombophilias**

- Inherited thrombophilias modestly increase the risk of maternal VTE.

- Most women (>95%) without a personal or family history of VTE will have uneventful pregnancies even when highly thrombogenic mutations are present.

- Risk of VTE increases (>10%) with a personal or family history of VTE or multiple defects.
Obstetrical and Fetal Risks of Maternal Thrombophilias
Retrospective Studies: Putative Associations

- Spontaneous abortion (SAB) embryonic loss at < 10 weeks
- Fetal loss > 10 weeks
- Abruption
- Preeclampsia
- IUGR
Rey at al., Lancet. 2003;361:901-8
Rey at al., Lancet. 2003;361:901-8
Link Between Thrombophilias & SAB < 10 weeks

Large European retrospective cohort study involving 571 women with thrombophilia having 1524 pregnancies vs. 395 controls having 1019 pregnancies found a significant association between any inherited thrombophilia and stillbirth (OR 3.6; 95% CI: 1.4-9.4) but not SAB (OR 1.3; 0.9-1.7).

Link Between Thrombophilias & SAB < 10 weeks

Large case-control study nested in a 32,700 cohort revealed an association between FVL and pregnancy loss after 10 weeks (OR 3.46; 95% CI 2.53-4.72) but not for losses occurring between 3 and 9 weeks.

Link Between Thrombophilias & SAB < 10 weeks

Retrospective cohort study of 491 patients with a history of adverse pregnancy outcomes:

• > 1 thrombophilia was protective of recurrent losses at < 10 weeks with ORs of 0.55 (95% CI: 0.33-0.92) and 0.48 (29-0.78), respectively.

• > thrombophilia was modestly associated risk of losses > 10 weeks [OR 1.76 (1.05-2.94) and 1.66 (1.03-2.68), respectively].

(Roque et al., Thromb Haemost. 2004; 91:290-5)
Association between MTHFR mutations and hyperhomocysteinemia and recurrent loss:

- Elevated fasting homocyst. level and RPL < 16 wks pooled OR = 2.7 (1.4-5.2)
- MTHFR & RPL (OR = 0.98 (0.5-1.72)

(Rey et al., Lancet. 2003;361:901-8; Nelen et al., Fertil Steril. 2000;74:1196-9)
# Prevalence of Inherited Thrombophilias in Women with Specific Obstetrical Complications vs. Controls.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Severe Preeclampsia (N=34)</th>
<th>Abruptio Placenta (N=20)</th>
<th>Fetal Growth Retardation (N=44)</th>
<th>Stillbirth (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with Thrombophilia</td>
<td>Odds Ratio (95% CI)</td>
<td>No. with Thrombophilia</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Factor V Leiden mutation, +/+ or +/−</td>
<td>9</td>
<td>5.3 (1.8–15.6)</td>
<td>5</td>
<td>4.9 (1.4–17.4)</td>
</tr>
<tr>
<td>Methylene tetrahydrofolate reductase mutation, +/+</td>
<td>7</td>
<td>2.9 (1.0–8.5)</td>
<td>3</td>
<td>2.0 (0.5–8.1)</td>
</tr>
<tr>
<td>Prothrombin mutation, +/−</td>
<td>2</td>
<td>2.2 (0.4–13.9)</td>
<td>4</td>
<td>8.9 (1.8–43.6)</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>5.4 (2.3–12.4)</td>
<td>12</td>
<td>7.2 (2.6–20.0)</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval, +/+ homozygous, and +/− heterozygous.

Meta-analyses of association of multiple thrombophilias with Preeclampsia (PE)

31 studies with 7522 patients were included:

• OR for FVL and PE = 1.81 (1.14-2.87) and for severe PE = 2.24 (1.28-3.94)

• No significant association with MTHFR or PGM

Meta-analyses of link between FVL & PE

- Studies published up to 2000 show an OR of 3.16 (95% CI: 2.04-4.92), but
- Studies published at and after 2001 show no association (0.97; 0.61-1.54)

(Kosmas et al., J Hypertens 2003;21:1221-8)
Meta-analyses of association of Hyperhomocysteinemia with Abruptio Placentalis

- Elevated Fasting homocysteine OR 5.3 (1.8-15.9)
- Homozygous MTHFR mutation OR = 2.3 - 2.6

Association between thrombophilia and IUGR

Among 493 cases with IUGR and 472 controls there was no significant association with:
- MTHFR C677T - OR 1.55 (0.83-2.90)
- MTHFR A1298C - OR 0.49 (0.25-0.93);
- FVL - OR 1.18 (0.54-2.55)
- PGM - OR 0.92 (0.36-2.35)

Prospective Studies Generally Demonstrate No Association with APO


- FVL: Prevalence of 3.61% (142/3,944) with no association found for PIH, PE-T, IUGR and fetal loss. However, FVL was associated with LGA (OR 1.81; 1.04-3.31) and mothers of 2 of 8 infants with neonatal deaths had FVL. *(Br J Haematol. 2008; 140:236-40)*
Prospective Studies Demonstrate
No Association with APO

APC resistance: Prevalence 11% (270/2480). APCR subgroup had no higher rate of APO than non-APCR patients, but did have an 8-fold higher risk of VTE (3/270 vs. 3/2210), a lower rate of intrapartum hemorrhage (3.7% vs. 7.9%) (p = 0.02), and less intrapartum blood loss (340 ml vs. 361 ml) (p = 0.04). (Thromb Haemost. 1999; 81:532-7)
Prospective Studies Demonstrate No Association with APO

PGM: 157 carriers among 4,167 patients with 1st tri. samples available (3.8%). Carriers had similar rates of pregnancy loss, preeclampsia, SGA, and abruption compared with non-carriers (Obstet Gynecol. 2010;115:14-20)

Inherited Thrombophias as a class: Found in 2034 nulliparas. PGM linked to composite APO* (aOR 3.6; 1.2-10.6); but only individual outcome linked to PGM was abruption (OR 12.2; 2.4–60.4) and there were only 9 patients had abruption. (Obstet Gynecol. 2010;115:5-13) * Fetal loss, severe preeclampsia, IUGR, abruption and NND.
Role of Ultrasound And Fetal Testing

- Prospective studies and large retrospective cohort studies show no link between thrombophilias and IUGR in low risk patients.
- However, it is unclear whether patients with prior adverse outcome (IUGR, PE-T, IUFD) and a thrombophilia are at increased risk for recurrence.
- While prophylactic treatment should be limited to RCTs, it may be reasonable to screen for IUGR in patients with thrombophilia and prior adverse pregnancy outcome.

(Paidas et al., Clin Perinatol. 2004 Dec;31(4):783-805)
How accurate is the clinical diagnosis of IUGR?

- With experienced examiners, Leopold maneuvers are as accurate as US measurements in EFW.
- But fundal height measurement alone is a poor predictor of EFW and limited as a screening method in the detection of FGR fetuses.
- Approximately 50% of IUGR fetuses are detected clinically, error in EFW by Leopold or ultrasound is 15 -20%.

• At the current time, US evaluation of the fetus is considered the standard for the diagnosis of IUGR.
• In addition to assessing the fetal weight to confirm the diagnosis of IUGR, US is also able to:
  – Confirm the gestational age
  – Rule out major fetal anomalies
  – Check amniotic fluid volume
  – Assess fetal status via the biophysical profile
  – Assess fetal blood flow via uterine artery Doppler and/or MCA Doppler
Recommendations: Women with prior APO and thrombophilia

- Serial sonograms are typically obtained at four week intervals, starting at 28 weeks. Persistent growth deficiency in multiple examinations over many weeks strengthens the likelihood of IUGR.
- Conversely, normal growth velocity in the otherwise small fetus is reassuring.
- **Umbilical artery Doppler**: It has been well established by RCTs that the use of umbilical artery Doppler velocimetry can reduce perinatal death as well as unnecessary induction of labor in the preterm growth restricted fetus.
Sample Management Algorithm

Suspected for SGA or FGR?

Ultrasound:
(1) Assess dating
(2) Estimated fetal weight
(3) R/O fetal anomaly
(4) R/O aneuploidy
(5) R/O genetic syndrome
(6) R/O infection

FGR confirmed?

1. Assess umbilical artery, middle cerebral artery, and ductus venosus Doppler flow weekly
2. Twice weekly NST/AFI
3. Repeat growth every 2 weeks

Deliver when:
1. Fetal compromise with a risk of intrauterine death as determined by fetal testing
2. Arrested growth
3. Greater than 38 weeks
4. Fetal lung maturity confirmed
5. Deterioration of an underlying maternal complication of pregnancy
Conclusions: Thrombophilia and Adverse Obstetrical and Fetal Outcomes:

- Many contradictory studies

- Appears to be a modest association between thrombophilia and fetal loss after 10 weeks in retrospective but not most prospective studies.
Association between Thrombophilia and Adverse Obstetrical and Fetal Outcomes:

- There is no convincing evidence of a link between thrombophilias and IUGR, or preeclampsia in either retrospective or prospective studies.
- There appears to be a modest link between hyperhomocysteinemia and abruption; and cannot R/O link between other inherited thrombophilias and abruption.
Thrombophilias: Maternal and Fetal Complications

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Recommendations

• Screening for thrombophilias in reproductive age women can be justified when there is a personal history of VTE associated with a non-recurrent risk factor. In this setting, the absence of a thrombophilia reduces the risk of occurrence or recurrence of VTE during pregnancy to a very low level while the presence of a thrombophilia mandates antenatal anticoagulation (B).
Recommendations

• Women with lower risk thrombophilias (*i.e.*, heterozygotes for FVL, PGM, PC or PS deficiency) who are without a history of prior VTE do not require antepartum treatment with prophylactic heparin but instead one should perform individualized risk assessment (C).
Recommendations

• There is no current support for screening for inherited thrombophilias in women experiencing recurrent unexplained fetal loss and other APO. Diagnosis and treatment regimens should only occur in context of IRB approved research protocol or where placental pathology is highly suggestive of a recurrent thrombotic disorder and no other etiology present (C).